II. Remarks

A. Status of the Claims

Claims 1-3, 6-8, 11-16, 18-22 and 24-25 are pending. Claims 4, 5, 9, 10, 17 and 23 were previously cancelled without prejudice. Claims 9 and 10 were previously cancelled. No amendments to the claims have been made.

B. Rejections under 35 U.S.C. § 103

i. Rejection over WO 89/09066

In the Office Action, the Examiner rejected claims 1-3, 6-8, 11-16 and 18-22 and 24-25 under 35 U.S.C. § 103 (a) as being unpatentable over WO 89/09066 (hereinafter "the '066 reference").

In making the rejection, the Examiner noted that "Applicants previously argued that the reference teaches away from the claimed high amounts of surface-active agent because WO states that above 50% by weight of surface-active agent, there is a phase inversion and may become a continuous phase." The Examiner further noted that "WO also states that the specific release of an active agent depends upon the active as well as the matrix components" and "WO also states that the active agent itself can have the surfactant properties." In view of the aforementioned, the Examiner concluded that "optimizing the amounts of the release controlling surfactants and polymers, so as to achieve the desired release rate, depending on the active agent used in the composition would have been obvious from the teachings of WO '066"

This rejection is traversed. With respect to independent claim 1, Applicants respectfully submit that the '066 reference fails in the very least to teach or suggest a dosage form, as recited in claim 1, wherein

> ...the weight ratio of hydrophobic fusible material to hydrophilic, organic polymeric wicking agent in said mixture is in the range from about 8:1 to about 16:1, wherein the dosage form provides, as tested by the Ph. Eur. Basket method at 100 rpm 900 ml aqueous buffer (pH 6.5) containing

> 0.05% w/w Polysorbate 80 at 37°C, an essentially zero order rate of release of the pharmaceutically active ingredient over a period of 8 hours, the amount of pharmaceutically active ingredient released over eight hours being in the range of 15% to 45%, and when tested in a group of at least five healthy humans the median tmax, based on blood sampling at half hourly intervals, is in the range of from about 2.5 to about 6 hours, and the ratio of mean Cmax to the mean plasma level at 24 hours is in the range of about 1.5 to about 3.5.

At the Examiner's own admission, the '066 reference "does not explicitly state the ratios of fusible materials to the polymeric wicking agent, release rates, dissolution parameters i.e., ratio of Cmax to mean plasma levels, tmax, W50 etc., and the claimed test method". See Office Action at page 3.

Further, the Examiner's attention is directed to page 8, line 24 to page 9, line 3, wherein the '066 reference describes that the maximum amount of surface active agent (asserted by the Examiner as a hydrophobic fusible material) is in an amount of about 2-50% by weight of the crystalline polymer (asserted by the Examiner as a hydrophilic, organic polymeric wicking agent) and the surface active agent. It is respectfully submitted that this ratio is at most a 1:1 ratio.

In contrast the ratio of hydrophobic fusible material to hydrophilic, organic polymeric wicking agent as recited in present claims 1 and 11 is in the range from about 8:1 to about 16:1. Further, although the Examiner asserts that the specific release of an active agent depends upon the active as well as the matrix components, the '066 reference describes that the surface active agent is typically present in the composition in an amount of about 2-50% when the active substance does not possess properties of a surface active agent and the surface active agent content of less than 2% may however be employed when the active substance possesses surface active agent properties. Further, it is stated in the '066 reference that if the content of the surface active agent exceeds about 50% there is a risk of a phase inversion.

In view of the aforementioned described in the '066 reference with respect to the surface active agent, it is respectfully submitted that one of ordinary skill in the art would not be motivated to formulate a dosage form having a ratio of hydrophobic fusible material to hydrophilic, organic polymeric wicking agent in the range from about 8:1 to about 16:1 as recited in the present claims. It is respectfully submitted that in view of the '066 reference, one of ordinary skill would only include the surface active agent (including the amount of active agent with surfactant properties as proposed by the Examiner) in an amount which does not exceed 50%, in order to avoid the risk of phase inversion. Thus, the '066 reference teaches away from the present invention.

Additionally, Applicants respectfully submit that the Examiner is using improper hindsight in suggesting that the pharmacokinetic parameters recited in claim 1 could be obtained via mere optimization. Pharmacokinetic parameters, e.g. Cmax and Tmax, vary with different formulations based on numerous factors, including the type, amount and ratios of active agent and excipients used. As stated above, the '066 reference fails to teach or suggest the claimed ratio of hydrophobic fusible material to hydrophilic, organic polymeric wicking agent. Therefore, it is only with the benefit of the disclosure of the present application that one skilled in the art would be motivated to prepare a formulation that provides the pharmacokinetic parameters recited in the present claims.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over the '066 reference be removed.

ii. Rejection over US 4,828,836

In the Office Action, the Examiner rejected claims 1-3, 6-8, 11-16, 18-22 and 24-25 under 35 U.S.C. § 103(a) as being unpatentable over the Elger reference, U.S. 4,828,836.

With respect to independent claims 1 and 11, Applicants respectfully submit that the Elger reference fails to teach or suggest the claimed dosage form wherein the ratio of

hydrophobic fusible material to hydrophilic, organic polymeric wicking agent is in the range from about 8:1 to about 16:1. At the Examiner's own admission, "Elger fails to teach exactly the same ratios as claimed, 8:1 to 16:1 and instead teaches a ratio of 1:4 to 4:1". See Office Action at page 5.

In support of her position that the presently claimed ratios, although not explicitly recited in Elger, would nonetheless be obvious over Elger, the Examiner states that the examples of Elger teach "a higher amount of hydrophobic polyethylene glycol as compared to polydextrose." See Office Action at page 5 (emphasis added).

Applicants respectfully submit herewith, as Exhibit A, a copy of Annunziata et al., "Effect of polyethylene glycol on the liquid-liquid phase transition in aqueous protein solutions", *PNAS* Vol. 99, No. 22 (Oct. 29, 2002) pp. 14165-14170. The Examiner's attention is directed to the first sentence of Annunziata et al., which states that "[p]olyethylene glycol (PEG) is a hydrophilic nonionic polymer...". Applicants respectfully point out that the Examiner's position is based on the erroneous assumption that polyethylene glycol is hydrophobic, when it is actually a hydrophilic polymer. Accordingly, the examples referred to by the Examiner do not teach or suggest a higher amount of hydrophobic fusible material to hydrophilic, organic polymeric wicking agent, and do not teach or suggest the ratio as recited in the present claims.

In view of the above, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over the Elger reference be removed.

C. Double Patenting Rejection

In the Office Action, the Examiner rejected claims 1-3, 6-8, 11-16, 18-22 and 24-25 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-33 of U.S. 5,965,163 (hereinafter "the '163 patent").

This rejection is traversed. Applicants respectfully submit that claims 1-33 of the '163 patent do not teach or suggest a dosage form wherein the ratio of hydrophobic fusible material to hydrophilic, organic polymeric wicking agent is in the range from about 8:1 to about 16:1 as recited in the present claims.

Further, Applicants respectfully submit that the dosage form recited in the claims of the '163 patent would not "inherently possess the ability to produce the claimed release rates", as suggested by the Examiner. It is respectfully submitted that pharmacokinetic parameters, e.g. Cmax and Tmax, vary with different formulations based on numerous factors, including the type, amount and ratios of active agent and excipients used. Applicants submit that the claims of the '163 patent fail to teach or suggest the ratio of hydrophobic fusible material to hydrophilic, organic polymeric wicking agent in the range from about 8:1 to about 16:1. Therefore, the dosage form recited in the claims of the '163 patent cannot inherently produce the claimed release rates.

Accordingly, Applicants respectfully request that the rejection under the judicially created doctrine of obviousness-type double patenting over the '163 patent be removed.

IV. Conclusion

It is now believed that the above-referenced rejection has been obviated and it is respectfully requested that the rejection. It is believed that all claims are now in condition for allowance.

According to currently recommended Patent Office policy the Examiner is specifically authorized to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

Respectfully submitted,
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